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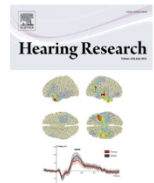
Carbamazepine induces upward frequency shifts of spontaneous otoacoustic emissions

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A B S T R A C T

In three subjects, we measured spontaneous otoacoustic emissions (SOAEs) when they were using carbamazepine (CBZ), and compared this to the SOAE measurement when they were not using CBZ. We observed 14 SOAEs showing a consistent upward shift of center frequency, related to CBZ intake. On average, the magnitude of the frequency shift increased with increasing frequency. The magnitude of the shift was 30–104 Hz, at frequencies ranging from 1.3 to 2.3 kHz, corresponding to a shift between 2.3 and 4.5%. Compared to other causes and manipulations known to change SOAE frequency, these shifts are relatively large. The underlying mechanism is most likely an increased stiffness of the cochlear partition. This would also explain the downward pitch shift due to CBZ, which has been reported by subjects with absolute pitch.

1. Introduction

Carbamazepine (CBZ) is a medical drug that is prescribed for epilepsy and neuropathic pain. It has common side effects like nausea and drowsiness, but can also have effects on hearing. Reported symptoms are tinnitus and hearing loss, although the effects of common dosages seem to be small (Hamed and Oseilly, 2018). Interestingly, CBZ is also prescribed as a treatment for typewriter tinnitus (Sunwoo et al., 2017).

A remarkable effect of CBZ is a change in pitch perception. Several case reports present patients noticing a lowered pitch due to CBZ intake (e.g., Fujimoto et al., 2004; Konno et al., 2003). Most of these subjects had absolute pitch and noticed a lowering of sound of about one semitone. Also, for most case studies, the effect was reversible, meaning that the pitch shift disappeared after stopping the CBZ intake. One study describes a detailed analysis in one subject —a professional concert pianist— taking CBZ (Chaloupka et al., 1994). The subject was asked to either sing a tone of a particular pitch, or to identify the pitch of a piano tone, synthesized by a computer. Production and identification of tones was measured before, during and after a period of taking the drug. The main outcome of this study was during CBZ use there was a downward pitch shift of about one semitone; the magnitude of the shift increased with increasing frequency.

The main mechanism of action of CBZ is that it modulates voltage-gated sodium channels, which prevents repetitive and sustained firing of action potentials and is therefore used as an anti-seizure drug (Sills and Rogawski, 2020). The mechanism by which CBZ changes the pitch is still unclear, although most authors of the case reports suggest a more central rather than a cochlear mechanism (e.g., Fujimoto et al., 2004). A spectral shift in the cochlea by a relative amount that increases with frequency would shift the tonotopic location of the higher harmonics of musical tones correspondingly, presumably making the sound inharmonic and rough in timbre (Braun and Chaloupka, 2005). Since timbre changes were not reported, the authors reason that a cochlear change is probably not causing the pitch shift in patients taking CBZ. They consider a change in the midbrain as a more plausible explanation.

In a study on long-term stability of SOAEs, it was shown that SOAEs show a downward frequency shift of, on average, 0.25%/year (Burns, 2009). The author notes that the magnitude of this shift coincides well with the pitch shift as reported by possessors of absolute pitch. Regarding the debate on whether pure-tone pitch is coded primarily by place or temporal information, Burns suggests measurements in subjects with both absolute pitch and SOAEs, when using CBZ. A first-order correlation between the shift of absolute pitch and the SOAE frequency shift would then suggest that place coding is dominant in pitch perception.

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Table 1

Subject characteristics and CBZ dose (in mg/day) at the different time points at which SOAEs were measured. For subject 1 and 2 two measurements were carried out, for subject 3 we performed three measurements. The measurements were performed at a time when the subjects had been taking the reported dose for at least a week. All three subjects were female. The third column indicates the number of SOAEs that were observed in the left and right ear, respectively. N.a.: not applicable.

Subject number	Age in years	Number of SOAEs [L;R]	CBZ dose at different measurements (mg/day)		
			Initial	After 2 months	After 3 months
1	35	[1;0]	0	400	n.a.
2	30	[4;4]	800	0	n.a.
3	33	[3;2]	900	100	0

In this study, we investigated possible cochlear changes due to the intake of CBZ. We did so by measuring otoacoustic emissions (OAEs) in patients that either started or stopped using CBZ. We used spontaneous otoacoustic emissions (SOAEs), since these OAEs can be measured with a high frequency resolution.

2. Material and methods

2.1. Subjects

We recruited subjects from the department of neurosurgery. We included patients that were either planning to stop using CBZ, or planning to start using CBZ. A further inclusion criterion was a relatively low age (between 18 and 45 years), to increase the chances of measuring SOAEs. The ethics board of the University Medical Center Groningen approved the study protocol. All participants provided written informed consent. The study followed the tenets of the Declaration of Helsinki.

We were able to measure SOAEs in three patients in whom CBZ was prescribed for trigeminal neuralgia (see Table 1). The maximum daily dosage across our subjects differed between 400 and 900 mg per day, respectively. SOAEs were recorded before and during (subject 1), or during and after (subjects 2 and 3) the drug was used. SOAEs were identified in five out of six ears.

2.2. Material

In two subjects, SOAEs were recorded in a soundproof room at the audiology department, with the subject sitting upright in a comfortable chair. A microphone probe (Etymotic Research ER-10C) was inserted in the ear canal, the gain of the system was set at 40 dB. The microphone signal was high pass filtered and amplified with a Stanford Research SR560 preamplifier. Signals were recorded with a ESI U24XL AD converter and analyzed off-line. Recordings were made of about three minutes per ear.

In one case (subject 1), SOAEs were recorded with the clinical Otodynamics Echoport 292 II equipment, running the ILOv6 software in SSOAE mode. This measurement was also performed in a soundproof room.

3. Results

We were able to measure SOAEs in three subjects (see Table 1). Five out of six ears showed SOAEs that were identifiable in all sessions. All together, 14 SOAE peaks were included. Fig. 1 shows an example of emission spectra from one ear, for three different CBZ dosages. All three SOAEs show a clear upward frequency shift of 2.8–3.1%, for a dosage increase from 0 to 900 mg/day.

In one patient (subject 3, see also Fig. 1), we were able to measure the SOAE for two different CBZ dosages. Fig. 2 shows the SOAE frequency shift of all 5 SOAEs of subject 3, for two different dosages: 100 and 900 mg/day (she started the treatment at 900 mg/day and then the dose dropped to 100 mg/day prior to terminating treatment). It makes clear that an increased CBZ dosage

gives an increased frequency shift. The average frequency shift was 0.71% for 100 mg/day, and 2.8% for the dosage of 900 mg/day. None of the subjects reported altered hearing during the CBZ intake.

Across all ears, CBZ caused an upward shift in SOAE frequency of 30–104 Hz, at frequencies ranging from 1.3 to 2.3 kHz. This corresponds to a shift between 2.3 and 4.5%, or between 39 and 76 cents. Since the dosage determines the frequency shift (see Fig. 2), and the dosages differed between subjects, we normalized the frequency shift. Fig. 3 shows the normalized frequency shift as a function of the SOAE center frequency without CBZ. Here, we left out the single data point of subject 1 because the dosage deviated substantially from subjects 2 and 3 (see Table 1), and different equipment was used for the measurement. The frequency shift was normalized to the average maximum dosage of subjects 2 and 3, being 850 mg/day. The magnitude of the frequency shift increased with increasing frequency. A linear fit through all data points (*Normalized shift = a*Center frequency+b*), yielded values $a = 0.00206\%$ and $b = -0.0347\%$/Hz, with *Normalized shift* in % and *Center Frequency* in Hz.

SOAE amplitudes also changed, due to CBZ intake. In contrast to the frequency changes, here, positive as well as negative changes were observed. The change in amplitude differed from -12.4 to $+11.0$ dB, with an average value of -0.5 dB (SD = 6.0 dB). Since it is known that the relative peak width of SOAEs is proportional to $1/\sqrt{\text{peak height}}$ (van Dijk et al., 2011), we examined whether this relation changed when our subjects were using CBZ. This turned out not to be the case (see Supplemental Fig. 1).

4. Discussion

In three subjects, we found 14 SOAEs showing a consistent upward shift of the center frequency, due to CBZ intake. On average, the magnitude of the frequency shift increased with increasing frequency. Also, in one subject, we could measure that the frequency shift increased with increasing dosage.

Case reports of subjects taking CBZ, describe them perceiving a downward pitch shift of around one semitone (see e.g., Fujimoto et al., 2004; Konno et al., 2003). As stated in the introduction, most of these subjects had absolute pitch. Possibly, people without absolute pitch are not able to observe the effect of a complete pitch shift, because they have no reference. Interestingly, the majority of case reports come from Japan. This may be related to the high prevalence of absolute pitch in Japan (Miyazaki et al., 2012).

The semitone shift was confirmed by the extensive psychophysical measurements in one subject, in which a downward shift in pitch was reported from about 20 cents at 33 Hz (C_1) increasing to 110 cents at 2.1 kHz (C_7) (Chaloupka et al., 1994). The CBZ dose for this subject was 400 mg/day. The cent is a logarithmic unit, used to measure musical intervals. An octave of 1200 cents is divided into 12 semitones of 100 cents each. As an example, increasing a tone of 1000 Hz by 100 cents would give a tone of $1000 \times 2^{(100/1200)} = 1059$ Hz. So an interval of 100 cents —or one semitone— equals 5.9%. To compare our findings with these psychophysical results, one has to take into account that in
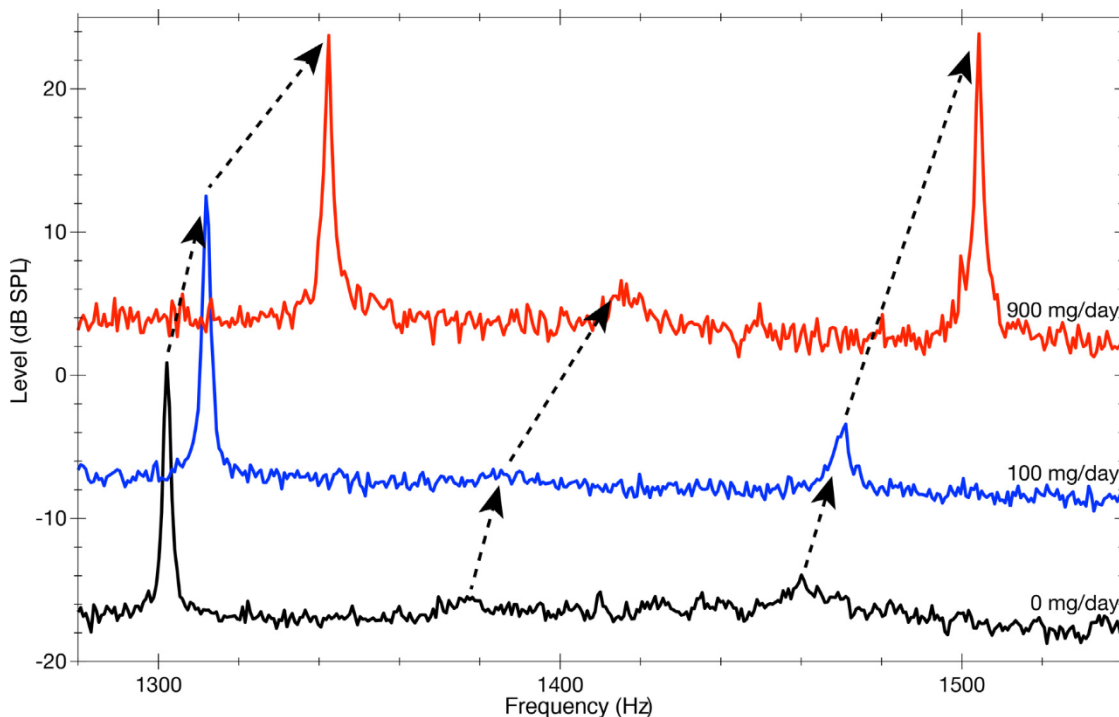
Fig. 1. Example of three SOAE spectra from one ear (subject 3, left ear), with the subject taking different doses of CBZ. The black, blue and red curves correspond, respectively, to the conditions with CBZ doses of 0, 100, and 900 mg/day (as indicated). The emission peaks were shifted upward by 40, 39, and 43 Hz, respectively (3.1, 2.8% and 2.9%). For clarity, the upper two curves were shifted vertically by 10 and 20 dB, respectively.
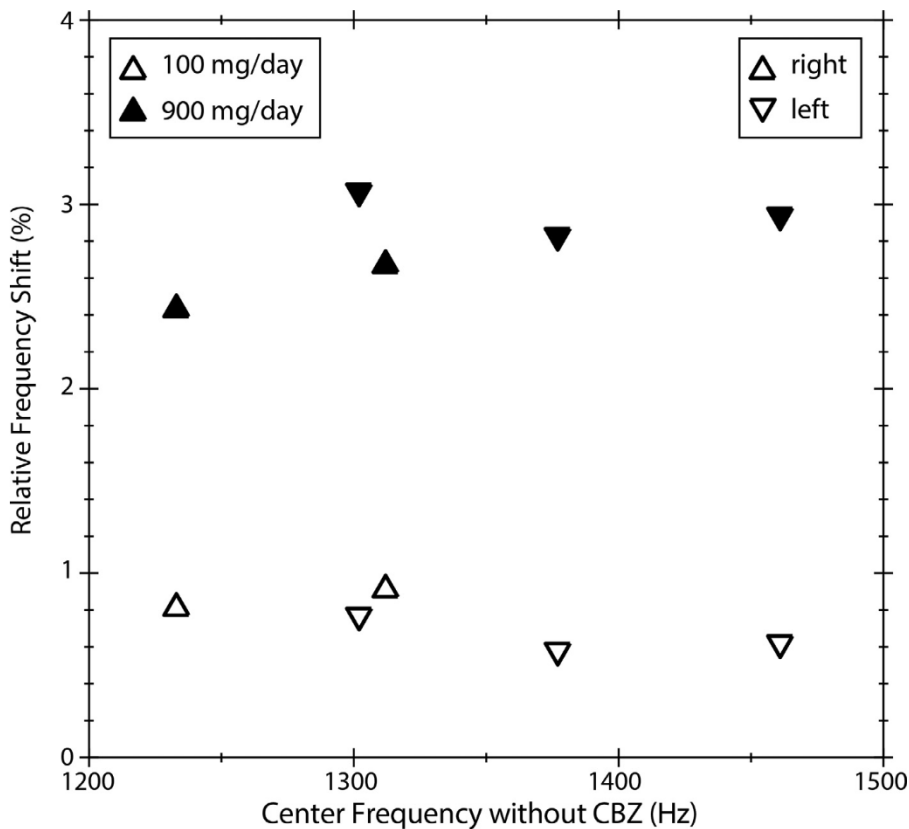
Fig. 2. Relative SOAE frequency shift as a function of frequency without CBZ, in one subject (subject 3), for two different CBZ dosages (as indicated in the legend). Downward (upward) pointing triangles indicate left (right) ears.
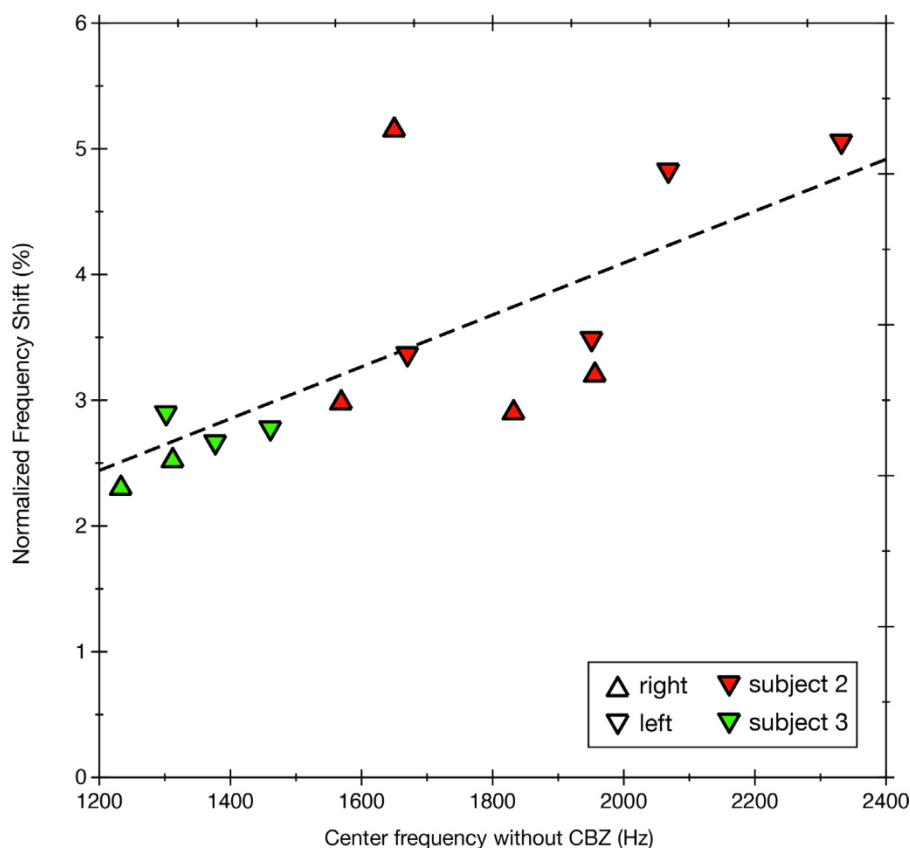
Fig. 3. Relative SOAE frequency shift due to CBZ, as a function of frequency without CBZ, for all SOAE peaks in subjects 2 and 3. Each ear is indicated with a different symbol (see legend). For a better comparison, the frequency shift was normalized to the average maximum dosage (850 mg/day). Dosages of the two subjects: S2 = 800, and S3 = 900 mg/day. The dashed line is a linear fit of all data points. A least squares fit of (*Normalized shift = a*Center frequency+b*), with *Normalized shift* in % and *Center Frequency* in Hz, yielded $a = 0.00206\%$ and $b = -0.0347\%$/Hz.

the latter case no pure tones were used. Instead, complex wave-forms were obtained by sampling piano tones. The fundamental frequency of these stimuli was used to denote the frequency of the stimulus. Still, it is not clear how pitch is exactly perceived; at the fundamental frequency or at the higher harmonics, and also whether time or place coding is most important (see e.g., Lau et al., 2017). Altogether, the magnitude of the negative pitch shift due to CBZ intake is between 1.7 and 5.9%, and is comparable to the positive frequency shift of the SOAEs we observed (between 2.3 and 4.5%).

Authors of the case reports hypothesize that the origin of the observed pitch changes must be either in the cochlea or somewhere in the central auditory pathway, where mostly a central mechanism is favored (Fujimoto et al., 2004; Konno et al., 2003). In a follow-up paper of Chaloupka et al. (1994), experiments with the same subject show results which are in favor of the changes occurring in the auditory midbrain (Braun and Chaloupka, 2005). The authors argue that for harmonic sounds (like the piano tones they used) a total spectral frequency shift in the cochlea would increasingly shift the higher harmonics. This would make the sound spectrum inharmonic and thereby rough in timbre, which was not reported by their subject and is also not mentioned in any of the case reports.

The upward frequency shift of SOAEs and the downward pitch shift in hearing —due to CBZ— may both be explained by a change in the mechanical properties of the cochlea. In a simple drawing, we show a section of the cochlea with neural connections (Fig. 4). Suppose the resonance frequency of a given cochlear location increases (as indicated by the altered color gradient). Then, at a certain location in the cochlea, the resonance frequency changes from,

say 2000 to 2100 Hz. Consequently: (1) the center frequency of the SOAE at that cochlear location increases from 2000 to 2100 Hz, and (2) an external tone of 2100 Hz will excite neurons that are tuned to 2000 Hz (assuming the neural contacts do not change). Regarding the perception of pure-tone pitch, there is still a debate between place or temporal information (Oxenham, 2013). The current findings suggest a role for place-coding.

Although SOAEs are very stable over time (the daily and monthly cycle show frequency shifts of less than 1% Bell, 1992), SOAEs can be manipulated. In several experimental ways, SOAE frequency was changed in humans (see Fig. 5). Most of these are based on changing the impedance of the middle ear, and thereby the SOAE frequency. This includes changes in ear canal pressure (Hauser et al., 1993), posture (de Kleine et al., 2000), and contraction of the middle ear muscles (Burns et al., 1993). In these experiments, SOAE amplitude in general decreases; frequencies mostly shift upward, although they may also go down. Changes are strongest for the lower frequencies (below 2 kHz). Contralateral acoustic stimulation (CAS) also induces changes in SOAEs, acting on the outer hair cells via the medial olivocochlear efferent system (Lewis, 2020). Although shifts are larger for stronger stimuli, they remain limited to about 1%. Presumably also acting via the outer hair cells, is the aftereffect of an intense low-frequency sound (Kugler et al., 2014). After the offset of a 30 Hz sound, a slow oscillation of SOAE amplitude and frequency is observed, lasting several minutes. In this case, an upward frequency shift is accompanied by an upward level shift. Finally, some changes in SOAE frequency are presumably caused by changes in the stiffness of the cochlear partition. These include changes due to aging, where SOAE frequencies decrease at about −0.25% per year consistent with a
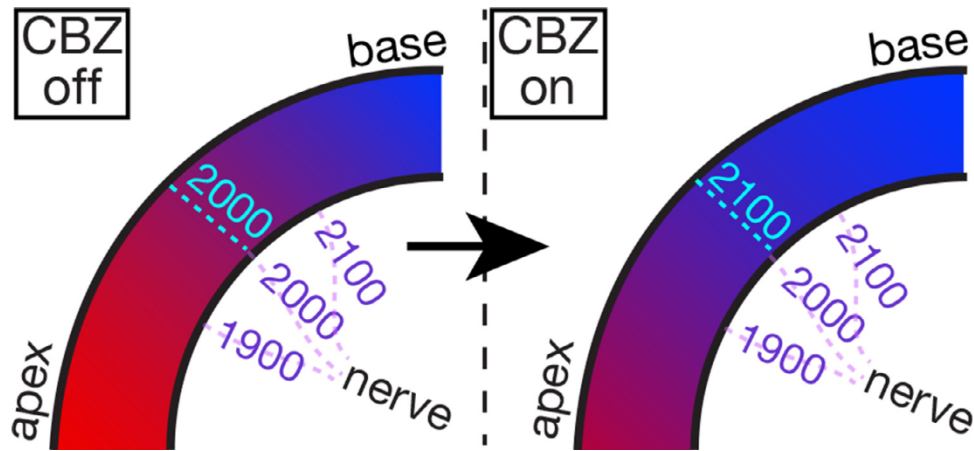
Fig. 4. Model of the observed changes. A small section of the cochlea with neural contacts (dotted lines), where the color gradient indicates the mechanical frequency to place distribution along the basilar membrane (with red representing the low frequencies and blue the high frequencies). Suppose the resonance frequency of the cochlear partition increases due to CBZ intake (comparing the left and right panels). Then, at a certain location in the cochlea, the resonance frequency changes from, say 2000 to 2100 Hz (indicated in cyan). Consequently (1) the center frequency of the SOAE at that cochlear location increases from 2000 to 2100 Hz, and (2) an external tone of 2100 Hz will excite the neural circuitry that corresponds to a 2000 Hz placecode, giving a 2000 Hz percept (assuming the neural contacts do not change).
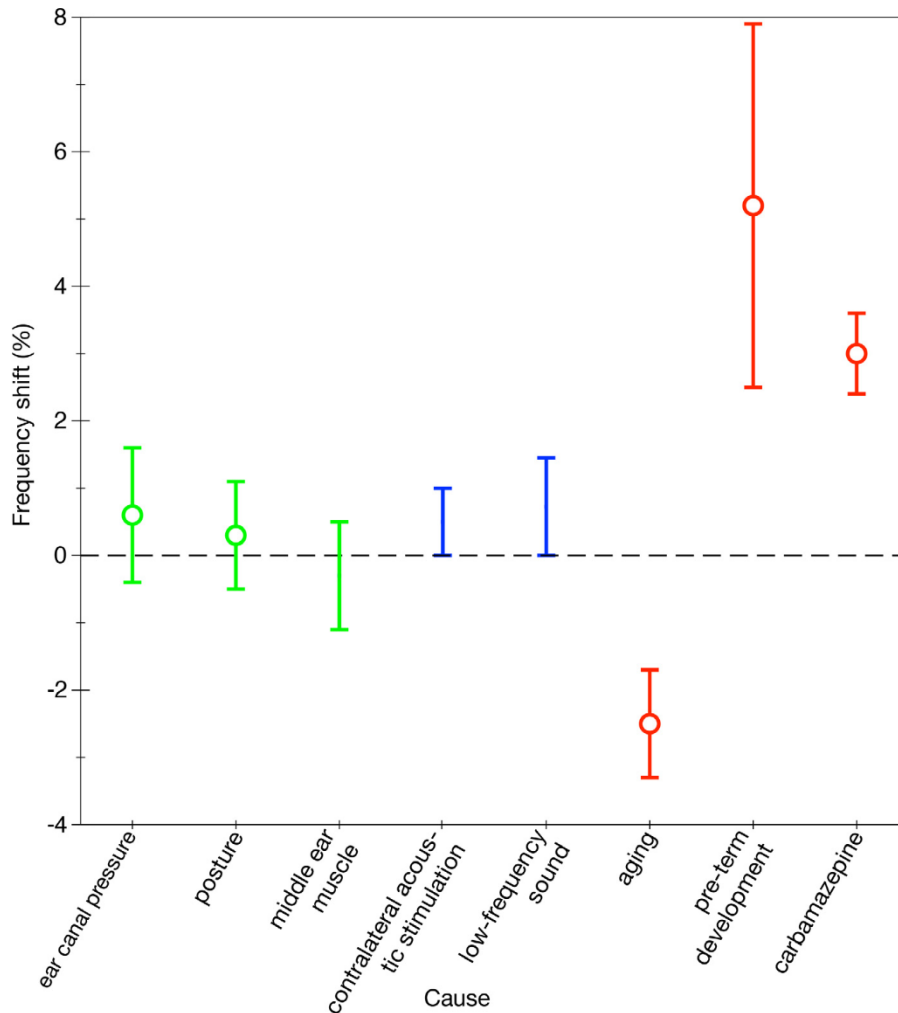
Fig. 5. Comparison of SOAE frequency shifts due to various causes. For each cause or manipulation, the mean frequency shift and standard deviation were plotted (point with error bar). When these numbers were not available, the total range was plotted (bar only). Causes: (1) ear canal pressure change from zero to +2 kPa (Hauser et al., 1993); (2) postural change from upright to head down 30° (de Kleine et al., 2000); (3) voluntary middle ear muscle contraction (Burns et al., 1993); (4) contralateral acoustic stimulation of 50 dB SPL (Lewis, 2020); (5) aftereffect of a low-frequency sound of 80 dB(A) (Kugler et al., 2014); (6) aging of 10 years (Burns, 2009); (7) preterm development between weeks 33 and 40 (Brienesse et al., 1997); (8) CBZ, between 400 and 900 mg/day [this study]. The colors indicate the underlying mechanism, as suggested by the authors: green = middle ear impedance, blue = outer hair cells, red = cochlear partition stiffness.

decrease in stiffness (Burns, 2009). Interestingly, preterm infants show the opposite: an increase in SOAE frequency (Brienesse et al., 1997). This increase was proportional to frequency with a mean rate of 0.74% per week, which would be consistent with an increasing stiffness.

Comparing all findings, we can conclude that manipulations acting via the middle ear impedance have much smaller effects than the CBZ effect described here (2.3–4.5%). Only the aging and pre-term developmental frequency shifts, which are probably due to mechanical changes in the cochlea, show shifts comparable to our findings produced by CBZ. The exact origin of the altered cochlear mechanics may lie in inner and outer hair cells, as well as in basilar and tectorial membranes. The supporting cells may also play a role (Raphael and Altschuler, 2003). Regarding the frequency decrease of SOAEs in the aging cochlea (Burns, 2009), a recent paper showed that in aging mice the group delay of distortion product OAEs becomes longer, suggesting an apical shift of the vibration pattern on the basilar membrane (Zhang et al., 2021). This was accompanied by a reduction of the size of the outer hair cells (OHCs) and a reduced level of prestin protein expression, which may explain the underlying mechanism. Taken together, these observations support an explanation for our findings based on changes in cochlear resonance frequencies.

The mechanism by which CBZ changes pitch and SOAE frequency is not clear. Since CBZ is prescribed for epilepsy, especially to prevent the occurrence of seizures, most studies focus on its action on brain excitability (Sills and Rogawski, 2020). CBZ is known to inhibit sodium (Na^+) channel activity, but it also inhibits calcium (Ca^{2+}) channels. It was concluded that CBZ does not act by a single mechanism, but may act at different levels like ion channels, receptors and signaling pathways (Ambrósio et al., 2002). CBZ is also used as a treatment for so-called typewriter tinnitus (Levine, 2006), which is probably neuro-vascular in origin. In this case, like other disorders such as trigeminal neuralgia and neuropathic pain, inhibition of the sodium channels leading to a decrease in neuronal activity is thought to be the main mechanism (Gambeta et al., 2020; Sunwoo et al., 2017). In order to understand the mechanism by which CBZ changes the inner ear mechanics, animal research may be helpful.

A limitation of the current study is the small group size we investigated. This is mainly because most patients taking CBZ are of older age and therefore have lower chances showing detectable SOAEs. Therefore, we selected patients starting or stopping with CBZ, aged 40 years or younger. A controlled study in healthy normal hearing volunteers could be of added value, although side effects of CBZ may give rise to ethical issues. Secondly, in addition to the SOAE measurements, we did not measure pitch shifts in our subjects, which would have been the ultimate goal. Our subjects did not possess AP, so the pitch shift experiments as performed by (Chaloupka et al., 1994)) were not possible to carry out. Absolute pitch is rare, so finding a subject with AP ánd using CBZ would be even more exceptional. On the other hand, pitch memory for well-known songs seems to be more widespread (Schellenberg and Trehub, 2003). This, in principle, opens the possibility of measuring SOAE and pitch shift in the same subject, as suggested by Burns (2009).

5. Conclusion

Carbamazepine caused relatively large upward frequency shifts for all spontaneous otoacoustic emissions. The underlying mechanism is most likely an increased stiffness of the cochlear partition. This would also explain the downward pitch shift due to CBZ, which is noted by subjects with absolute pitch.

Declaration of Competing Interest

The authors declare no competing financial interests.

CRediT authorship contribution statement

Emile de Kleine: Visualization, Investigation, Formal analysis, Writing – review & editing. **Bert Maat:** Visualization, Investigation, Formal analysis, Writing – review & editing. **Jan D. Metzemaekers:** Writing – review & editing. **Pim van Dijk:** Visualization, Investigation, Formal analysis, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.heares.2022.108492.

Supplementary Fig. 1. Relative peak width versus peak height, where the open (respectively closed) symbols represent the SOAE peaks with the subjects being off (respectively on) CBZ. Subjects 2 and 3 are denoted by circles and diamonds, respectively. SOAE peak parameters were determined by fitting a Lorentz curve to the spectrum, using a least-squares method. This yielded the peak height in mPa^2/Hz, the peak width (Δf) and center frequency (f_0) in Hz. The dashed line indicates the relationship between SOAE peak width and height, being that the relative width, $\Delta f/f_0$, is proportional to $1/\sqrt{peak\ height}$. This relationship does not deviate from that published previously (van Dijk et al., 2011, Fig. 8).

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